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(54) Title: AN ORAL FORMULATION FOR GASTRIC ANTIBACTERIAL TREATMENT AS WELL AS A PROCESS THEREOF AND THE USE

(57) Abstract

An oral formulation with extended release for treatment of infections in the upper gastrointestinal tract as well as processes for the preparation and the use thereof.

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AN ORAL FORMULATION FOR GASTRIC ANTIBACTERIAL TREATMENT AS WELL AS A PROCESS THEREOF AND THE USE

Technical field

The invention relates to formulations for treatment of infections in the upper gastrointestinal tract especially infections caused by Helicobacter pylori, and a process for the manufacture of said formulations as well as the use thereof.

Said formulations give a prolonged release of antimicrobal agent(s) in the upper gastrointestinal tract.

Background of the invention

Helicobacter pylori (H.pylori) is a recently discovered bacterium, cultured for the first time in Australia 1982 [Warren JR Lancet 1983;1:1273], which has attracted much interest due to its possible aetiological role in a number of disorders in the upper gastrointestinal tract. It is considered a major cause in the development of peptic ulcer disease [Helicobacter pylori Working Party Report. World Congress in Gastroenterology, Sydney 1990] H. pylori is accepted as the aetiological agent in most cases of chronic non-specific gastritis. Chronic active gastritis is highly correlated to H. pylori-infections. The organism is found in association with chronic active gastritis in almost 100% of the cases. Further, it was concluded in a case-control study of 372 patients that infection with H. pylori is associated with an increased risk of gastric adenocarcinoma and may be a cofactor in the pathogenesis of this malignant condition [Parsonnet J, Friedman GD, Daniel MS et al. N Engl J Med 1991;325:1127-31].

The pathogenic mechanism of H. pylori is not yet known in its

details. The mode of transmission is unknown but considered to be by the faecal oral route and may be waterborne. H. pylori is found throughout the world but there is a higher prevalence of the organism in less developed countries and in patients with low economic status in western countries. The overall prevalence in western countries is about 52 % and increases with advancing age.

H. pylori is a Gram-negative microaerophilic bacterium which is about 3.5 µm in length and 1 µm in diameter. Due to the presence of 4-6 flagella attached to the end of its typical S- or spiral shape form, the bacterium can move rapidly in mucus. It lives closely attached to the gastric epithelial cells beneath the mucus layer and colonises the stomach, mainly the antrum, in a patchy fashion.

In vitro studies show a high sensitivity of H. pylori to many antibiotics [McNulty CA, Dent JC. Eur J Clin Microbiol Infect Dis 1988;7:566-569], [Lambert T, Megraud F, Gerbaud G et al. Antimicrob Agents Chemother 1986;30:510-511]. However, in vivo studies have demonstrated that there is a small correlation between in vitro sensitivity for H. pylori and treatment results in vivo for antibacterial drugs. The eradication regime with best eradication results today (elimination of H. pylori in 80-90% of treated patients) is triple therapy [Axon ATR. Scand J Gastroenterol 1989;24(suppl 160) :35-38.]. The therapy is a combination of a bismuth preparation, metronidazole and amoxicillin or tetracycline. However, the dosage regimen involves many tablets and there is a need of administration several times per day. This is difficult for the patient to follow and compliance has been shown to be important to achieve the high eradication

rates. Adverse effects, mainly due to metronidazole or bismuth are very common. About 30% of the patients have reported side effects [Axon ATR, Scand J Gastroenterol 1989;24(suppl 160):35-38].

Monotherapy of different antibiotics which are known to have good effect in vitro against H.pylori is insufficiently effective in vivo. Amoxicillin, for example, eradicates H.pylori only in about 20% of treated patients. Combination of two drugs give higher eradication rates than monotherapy. Bismuth preparations (bismuth subsalicyclate or colloidal bismuth subcitrate) in combination with amoxicillin eradicated H.pylori in 44 % of treated patients, bismuth + metronidazole, amoxicillin + tinidazole and amoxicillin + metronidazole in about 55 % of the patients, respectively [Chiba N, Rademaker JW, Rao BV et al. Gut 1991;32:A1220-1221 Abstract].

Antibacterial agents have also been combined with acid secretion inhibitors. Combinations with histamin$_2$-blockers show no improved effect. Proton pump inhibitors e g omeprazole, which have very little anti-H.pylori effect on its own show a synergistic effect in combination with antibiotics. A dose of 750 mg amoxicillin twice daily with 40 mg omeprazole once daily was reported to eradicate H.pylori in 54% of the patients [Unge P, Eriksson K, Bergman B. et al. Gastroenterol 1992;102(4);A183(abstract)]. Any explanation for this synergistic effect is not yet known, according to available information.

Many antibiotics have relatively short duration of action and are given 3-4 times a day. Attempts to prolong the action by use of prolonged release products have generally been unsuccessful

because the absorption of the antibiotic from the gastrointestinal tract is poor when administered in slow release form [Delgado Charro MB, Vila Jato JL. Int J Pharm 1992;78;35-41] Instead antibiotics are given in rapidly absorbed formulations, e g tablets or capsules. In order to achieve sufficiently long duration of action higher doses are given.

In all previous studies on H.pylori eradication rapidly available dosage forms of the antibacterial agents have been used and attempts have been made to increase the success rate by using very high doses of antibacterials as well as proton pump inhibitors. For example, 82% of treated patients were eradicated after 10 days therapy of 40 mg omeprazole twice daily in combination with 1 g amoxicillin twice daily followed by 6 weeks monotherapy of 20 mg omeprazole once daily.[Bayerdörffer E, Mannes GA, Sommer A et al. Gastroenterol 1992;102(4):A38(abstract)].

Outline of the invention

We have discovered that the effectiveness of the treatment can be improved in an entirely different way, namely by administration of the antibacterial agents in prolonged release formulations and administer the formulations in such a way that they stay in the stomach several hours. It is not yet known if the H.pylori bacterias are accessible for treatment by antibacterial agents in the stomach or if the drug has to be absorbed and reach the bacterias via the blood circulation. The improved effect of formulations according to this invention may indicate that a local effect in the stomach is important.

Examples of formulations with prolonged gastric residence time

are bioadhesive systems which interact with mucus or the mucosa. Another way to prolong the residence time is swelling systems which expand in contact with the gastric fluid to a size which does not allow the system to pass through the pylorus. Further examples are formulations with very high density or systems which float on the gastric contents. It has also been observed that large non-disintegrating tablets or capsules can be retained for several hours in the stomach. The retention time in the stomach is especially prolonged when the tablet or capsule is administered together with food due to the sieving function of pylorus when the stomach is in the digestive mode [Davis SS, Hardy JG, Taylor MJ et al. Int J Pharm 1984;21:331-340]. Food also retards the emptying of tablets or pellets, but the effect is less pronounced. The critical size is reported to be about 7 mm [Khosla R. Nottingham: University of Nottingham, 1987.(Diss).]

The drug should be released within 1-24 h, preferably 1-6 h. To achieve an effective treatment of H.pylori infection the product should remain in the stomach at least 2-4 h, preferably more than 6 h. The major part of the drug should be released before the tablet leaves the stomach. The drugs suitable for the preparations according to the invention are e.g. ampicillin, amoxicillin, benzylpenicillin , phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, methicillin, oxacillin, piperacillin, ticarcillin,flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalexin, cefaclor, cefadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin, dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin,

tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoxazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, mecillinam, cloxiquine, chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol. The active agents could be in standard forms or used as salts, hydrates, esters etc. A combination of two or more of the above listed drugs may be preferable, for example to minimize the risk for developing resistance. The antimicrobial agents can also be combined with other drugs used in the treatment of acid related diseases e.g. acid pump inhibitors or H_2-blockers, such as for example omeprazole.

Possible formulations to be used are large non-disintegrating tablets or capsules e.g. inert matrix tablets [Hui H, Robinson JR, Lee VHL. Design and fabrication of Oral Controlled Delivery Systems. In: Robinson JR, Lee VHL, eds. Controlled Drug Delivery. Fundamentals and applications. New York: Marcel Dekker, Inc, 1987:373-432], osmotic pumps [Davis SS, Fara JW. Osmotic pumps. In: Hardy JG, Davis SS, Wilson CG, eds. Drug Delivery to the Gastrointestinal Tract. Chichester: Ellis Horwood Limited, 1989:97-109.] and membrane-coated tablets. Further, swelling systems [Banker, US Patent + no 261,242,] floating systems [Davis SS, Stockwell AF, Taylor MJ et al. Pharm Res 1986;3:208-213.], [Washington N, Wilson CG, Greaves JL et al. Scand J Gastroenterol 1988;23:920-924], formulations with high

density [Devereux JE, Newton JM, Short MB. J Pharm Pharmacol 1990;42:500-501] and mucoadhesive systems [Junginger HE. Pharm Ind 1991;53:1056-1065] prepared from e.g. polycarbophil, polyacrylic acid, methylcellulose, polyethylene oxide, chitosan, tragacanth, sodium carboxymethyl cellulose can be used.

An example from the above listed formulations is the inert porous matrix tablet which is obtained by mixing the drug with waxes or water insoluble polymers and with fillers and binders. Paraffin, polyvinylchloride, ethylcellulose, stearylic alcohol, cetylic alcohol, carnauba wax, polyethylene, polyvinyl acetate, polymethyl methacrylate could be used as suitable diffusion retarding compounds. Other excipients used in the preparations of such tablets are e.g. lactose, mannitol, calcium phosphates, magnesium stearate, hydroxypropyl methylcellulose, methylcellulose, polyvinylpyrrolidone, aluminium silicate, sodium carbonate, potassium phosphate or other suitable materials.

Examples

It is the object of the present invention to provide an extended-release preparation with prolonged gastric residence time after oral administration, containing one or more antimicrobial agents.

Example 1:	g
Amoxicillin sodium	830
Paraffin	500
Ethylcellulose	60
Magnesium stearate	28.8

Amoxicillin sodium was mixed in a planetary mixer for 5 minutes with paraffin. The resultant mixture was then moistened for 5 minutes with a solution of ethylcellulose in isopropanol and dried. The granulate was milled through a 1.0 mm sieve and lubricated for 2 minutes with magnesium stearate.

The granulate was compressed to tablets on a tabletting machine fitted with 13 mm punches. Each tablet contained 415 mg amoxicillin sodium. The release profile of the drug is shown in Figure 1.

Example 2:	g
Amoxicillin trihydrate	215.6
Paraffin	250
Sodium carbonate	209
Ethylcellulose	30
Magnesium stearate	14.1

The composition according to Example 2 was formed to modified release tablets containing 375 mg of amoxicillin/tablet. The tablet were prepared in the following way:

Amoxicillin trihydrate, paraffin and sodium carbonate were mixed for 5 minutes in a planetary mixer. The remaining process was made according to Example 1. The release profile of the drug is shown in Figure 2.

Example 3	g
Amoxicillin trihydrate	215
Tripotassium phosphate	209
Polyvinylpyrrolidone	20
Magnesium stearate	20

Compressed into tablets after granulation and drying as in Example 1. The tablets were coated with a porous membrane coating consisting of polyvinyl chloride in acetone according to [Källstrand G, Ekman B. J Pharm Sci 1983;72(7):772-775]. Micronized sucrose (particle size less than 10 um) was suspended in the polymer solution. Coating was achieved by spraying the suspension on a moving bed of tablets with an airless sprayer. Coating was continued until the weight if the coat on each tablet was 50 mg.

Example 4:	g
Amoxicillin trihydrate	244
Ethylcellulose	268
Chitosan	366
Hydrochloric acid	0,13
Water purified*	q.s.
Ethanol*	q.s.

*Used in the manufacture of pellets but removed during subsequent processing

The bioadhesive pellets were manufactured using conventional fluid-bed coating technology. Amoxicillin trihydrate was successively coated with solutions containing chitosan and ethylcellulose, respectively.

Claims

1. An oral formulation containing active materials for treatment of infections in the upper gastrointestinal tract characterized in that the formulation is retained in the stomach for a prolonged time whereby the active materials are released continuously during said time.

2. A formulation according to claim 1 where the preferred retention time is at least 1 h during which period the active materials are released continuously.

3. A formulation according to claim 1, wherein the formulation contains one or more antibacterial agents.

4. A formulation according to claim 1 where the infection is caused by Helicobacter pylori.

5. A formulation according to claim 1 wherein the active substance is amoxicillin.

6. A formulation according to claim 1 comprising a combination of two or more active agents.

7. A formulation according to claim 1 where the dosage form has bioadhesive properties.

8. A formulation according to claim 1 consisting of a non-disintegrating prolonged release formulation containing antibacterial agents.

9. A formulation according to claim 8 wherein the size is not less than 7 mm.

10. A formulation according to claim 9 where the release of the active compound is controlled by a non-disintegrating membrane.

11. A formulation according to claim 9 where the formulation is an inert porous matrix.

12. A process for the manufacture of a preparation according to claim 11 wherein the active substance is mixed with polymers or materials in an amount exceeding 10% of the weight of the mixture and the resulting mixture is compressed into a tablet.

13. A process according to claim 12 wherein the tablet is heated to a temperature above the melting point of the waxy material to retard the release profile and improve the mechanical strength of the tablet.

14. Use of a formulation according to claim 1 in the preparation of an active dosage form for the treatment of infections in the upper gastrointestinal tract.

15. Use of a formulation according to claim 1 together with acid secretion inhibitors.

16. Use of a formulation according to claim 1 together with proton pump inhibitors.

17. Use according to claim 16 wherein the proton pump inhibitor is omeprazole.

EXAMPLE 1 PHOSPHATE BUFFER, pH 4.5, 100 rpm

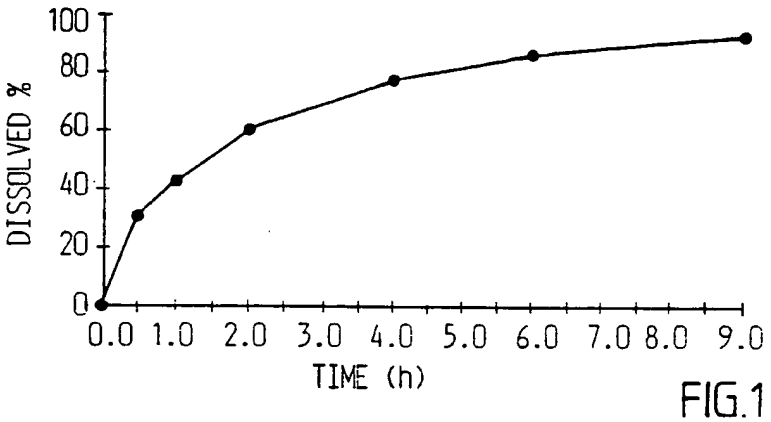

FIG.1

EXAMPLE 2 PHOSPHATE BUFFER, pH 4.5, 100 rpm

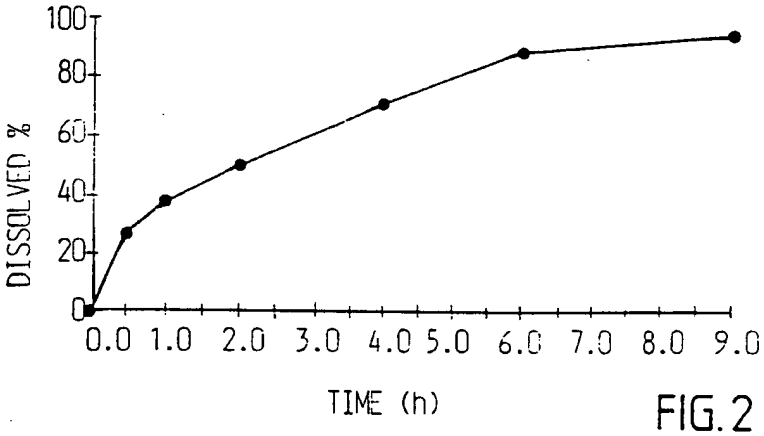

FIG.2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00521

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/22, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS,EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0490450 (BROCADES PHARMA B.V.), 17 June 1992 (17.06.92), see page 2, line 1 - line 47; page 7, line 40 - line 49; example 5; claims 11-15	1-6,14-17
X	WO, A1, 9119486 (KALMO ENTERPRICES, INC.), 26 December 1991 (26.12.91), see page 9, line 4 - page 10, line 17; claims 1-6	1-8
X	EP, A2, 0455475 (RECKITT AND COLMAN PRODUCTS LIMITED), 6 November 1991 (06.11.91), see page 2 - page 3, line 47, claims	1-4,7-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Current Opinion in Gastroenterology, Volume 8, 1992, C.S. Goodwin et al, "Peptic ulcer disease and Helicobacter pylori infection" page 122 - page 127 --	1-17
E,A	Dialog Information Services, file 154, MEDLINE, Dilaog accession no. 08302546, MEDLINE accession no. 93012546, Rune S: "Helicobacter pylori, peptic ulcer disease and inhibition of gastric acid secretion", Diqestion (SWITZERLAND) 1992, 51 Suppl 1 p11-6 -- --------	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/08/93

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0490450	17/06/92	AU-A- 9134791	08/07/92
		WO-A- 9210502	25/06/92
WO-A1- 9119486	26/12/91	AU-A- 8219191	07/01/92
EP-A2- 0455475	06/11/91	AU-A- 7596891	07/11/91
		GB-A- 2243549	06/11/91